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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/629,318	07/28/2003	Andrew P. Feinberg	JHU1900-1	6572

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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/629,318	FEINBERG, ANDREW P.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,7-18 and 20-22* is/are pending in the application.

4a) Of the above claim(s) *21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,7-18,20 and 22* is/are rejected.

7)☒ Claim(s) *9,12 and 22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. This action is responsive to the Amendment and Response filed November 2, 2009. Claims 1, 3, 10, 14, 17, and 20 have been amended, claims 2 and 5-6 have been canceled, and claim 22 has been added. Claim 21 remains withdrawn (see below) and claims 1, 3-4, 7-18, 20 and 22 are now under consideration. Any rejections and/or objections not reiterated in this action have been withdrawn. In particular, it is noted that all rejections of claims 2 and 5-6 set forth in the prior Office action are moot in view of the cancellation of those claims, and that applicant's amendments have overcome several rejections under 35 USC 112, second paragraph set forth in the prior Office action. However, regarding the rejection under 35 USC 112, first paragraph for lack of enablement set forth in the prior Office action, Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons given below. Additionally, applicant's amendments have necessitated the new grounds of rejection set forth below. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

3. This application contains claim 21 drawn to an invention nonelected with traverse in the reply filed on April 26, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. It is also again noted that, with regard to claim 9, the elected species

of SEQ ID NOs 2-3 is under consideration herein (see reply filed on December 26, 2008, as well as the election/restriction mailed October 29, 2008).

Claim Objections

4. Claims 9, 12, and 22 are objected to because of the following informalities: claim 9 depends from a claim that has now been canceled; claim 12 recites "the methods" rather than "the method"; claim 22 fails to end in a period. Appropriate correction is required.

5. In view of the cancellation of claim 2, claim 9 has been treated as dependent on claim 1 for purposes of examination herein.

Claim Rejections - 35 USC § 112, second paragraph

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANT'S AMENDMENTS:

6. Claims 17-18 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17-18 and 20 are indefinite over the recitation of the limitation "the IGF2 gene" in lines 4-6 of claim 17. There is insufficient antecedent basis for this limitation in the claims, as claim 17 has been amended to reference "an IGF2 DMR" (whereas the claim previously referenced "an IGF2 gene"). Accordingly, correction/clarification is required.

Claim Rejections - 35 USC § 112, first paragraph – new matter

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANT'S AMENDMENTS:

8. Claims 1, 3-4, 7-18, 20 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

Applicant has amended independent claims 1, 10, and 17 to require that "hypomethylation is as compared to the half-methylation of the normally imprinted gene." While the originally filed specification does disclose hypomethylation as compared to (or relative to) half-methylation (as referenced in the paragraph identified by applicant [paragraph 181] and as is additionally referenced/disclosed in, e.g., Tables 3 and 4), the specification does not disclose the concept of "half-methylation of the normally imprinted gene," i.e., does not disclose or define a "normally imprinted gene" as being a half-methylated gene. In fact, paragraph 181 (referenced by applicant in supporting the amendment of the claims) provides examples of cases in which imprinting of H19 and methylation of that gene are not related or not clearly related. Further, while the specification references examples in which imprinting of IGF2 and methylation of that gene are linked/related (par 181), the specification does not appear

to provide any disclosure of the concept of "normal" imprinting as requiring half methylation with respect to either H19 or IGF2. Accordingly, applicant's amendments introduce new matter into the claims.

Claim Rejections - 35 USC § 112, first paragraph - enablement

9. Claims 1, 3-4, 7-18 and 20 remain rejected, and new claim 22 is now rejection, under 35 U.S.C. 112, first paragraph, for the reasons given in the prior Office action of May 1, 2009. A**pplicant's amendments have necessitated the inclusion of new claim 22 in this rejection.**

It is noted that applicant's amendments have overcome portions of the rejection of record. Specifically, the claims as amended now clearly require detection of hypomethylation of a DMR "as compared to" half-methylation (although the reference to "half-methylation of the normally imprinted gene" raises a new matter issue, as indicated above). Further, the claims now require that the DMR of IGF2 "comprises SEQ ID NO: 1," and the claims no longer encompass fragments or polymorphisms of SEQ ID NO: 1 or of SEQ ID NO: 6 (the DMR of H19 referenced in the claims). However, as the amended claims continue to lack enablement for reasons already of record (see the rejection of May 1, 2009), this rejection has been maintained. Regarding new claim 22, it is noted that those aspects of the original rejection that apply to claim 1 (from which claim 22 depends) also apply to claim 22; however, it is noted that claim 22 is limited to 2 types of samples that are considered enabled as described in the original rejection.

The response of November 2, 2009 traverses the rejection on the following grounds.

The response argues that the claims as amended are fully enabled, noting that the invention "is based on the discovery in the present application that hypomethylation, rather than hypermethylation, is linked to the LOI of IGF2 in colorectal cancer." In response, it is noted that applicant's amendments have in fact overcome some aspects of the original rejection (as noted above), and that the specification is in fact considered enabling with respect to a particular type of hypomethylation in specific sample types in human CRC patients, as indicated in the original rejection.

The response summarizes the "two lines of evidence" provided in the specification with regard to the association of hypomethylation with LOI of IGF2 in colorectal cancer, citing data obtained using CRC cell lines and in primary human CRC, and summarizing the human data provided in the specification. The reply further cites a "recent report by Murrell et al (PLOS One 3(3):e1849, 2008) (copy attached to the reply but not cited) as supporting applicant's findings, noting that "the authors evaluated the same IGF2 DMR (termed "DMRO"), including the same 3 CpG, as well as 3 others within this MDR, and found that hypomethylation was associated with LOI of IGF2." These arguments have been thoroughly considered but are not persuasive. Regarding the Murrell et al reference, it is noted that an application must be enabling with respect to a claimed invention as of the time the invention was made; the Murrell et al reference, published several years after applicant's filing date, cannot be relied upon with regard to the state of the art, or the enablement of the claimed invention, at the relevant point in time. Further, it is again noted that the rejection does not dispute the enablement of the invention with respect to hypomethylation at the particular sites exemplified by applicant

(i.e., the sites referenced in the response). However, neither the specification nor the prior art actually establishes that applicant's findings at these particular sites actually reflect a broader pattern. It is particularly noted that the reply does not address any of the prior art references cited in the rejection, which suggest, e.g., both hypermethylation (rather than hypomethylation) in association with cancer (in a gene encompassed by the claims)(Nakagawa et al), as well as a lack of association between hypomethylation and LOI in cancer (Ahomadegbe et al, as well as Ito et al). Accordingly, applicant's arguments are not persuasive.

Finally, the reply argues that applicant's cell lines "are colorectal carcinoma cells, and as such would be recognized by the skilled artisan as relevant to the study of colorectal cancer," and that the fact that HCT116 cells undergo LOI of IGF2 after being genetically engineered to produce hypomethylation supports "the role of hypomethylation in LOI of IGF2". These arguments have also been thoroughly considered but are not persuasive. Again, it is acknowledged that applicant has established that hypomethylation of particular sites in SEQ ID NO: 1 actually occurs in human patients in association with LOI of IGF2 in CRC; thus, the fact that hypomethylation of some sites in IGF2 plays a role in LOI of IGF2 in human patients is not in dispute. However, the fact that hypomethylation can be artificially induced in cells to produce LOI of IGF2 does not mean that such a generalized type of hypomethylation actually occurs in association with LOI in cancer patients, and one skilled in the art would not draw such a conclusion in the absence of actual evidence. Applicant has not provided actual evidence that the genetically engineered cells exemplified in the

specification actually reflect *in vivo* patient status. Accordingly, these arguments are not persuasive.

This rejection is maintained.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday-Friday, 8:30 am-2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571/272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634